Cerebral perturbations during exercise in hypoxia.

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INVITED REVIEW:

CEREBRAL PERTURBATIONS DURING EXERCISE IN HYPOXIA

Running head: The brain during hypoxic exercise

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ABSTRACT

Reduction of aerobic exercise performance observed under hypoxic conditions is mainly attributed to altered muscle metabolism due to impaired O_2 delivery. It has been recently proposed that hypoxia-induced cerebral perturbations may also contribute to exercise performance limitation. A significant reduction in cerebral oxygenation during whole-body exercise has been reported in hypoxia compared to normoxia, while changes in cerebral perfusion may depend on the brain region, the level of arterial oxygenation and hyperventilation-induced alterations in arterial CO_2. Using transcranial magnetic stimulation, inconsistent changes in cortical excitability have been reported in hypoxia, while a greater impairment in maximal voluntary activation following a fatiguing exercise has been suggested when arterial O_2 content is reduced. Electromyographic recordings during exercise showed an accelerated rise in central motor drive in hypoxia, probably to compensate for greater muscle contractile fatigue. This accelerated development of muscle fatigue in moderate hypoxia may be responsible for increased inhibitory afferent signals to the central nervous system leading to impaired central drive. In severe hypoxia (arterial O_2 saturation <70-75%), cerebral hypoxia *per se* may become an important contributor to impaired performance and reduced motor drive during prolonged exercise. This review examines the effects of acute and chronic reduction in arterial O_2 (and CO_2) on cerebral blood flow and cerebral oxygenation, neuronal function and central drive to the muscles. Direct and indirect influences of arterial deoxygenation on central command are separated. Methodological concerns as well as future research avenues are also considered.

Keywords: cerebral perfusion, cerebral oxygenation, cortex excitability, central motor command, endurance

INTRODUCTION

With the exception of very short or static exercises performed at a high percentage of maximal power (15, 19, 83), hypoxia deteriorates exercise performance (7, 82). In particular, the maximal aerobic workload ($\dot{W}_{max}$) that can be sustained during exercise involving large muscle groups (*e.g.* cycling) is considerably lower in hypoxia compared to normoxia. The difference between these two environmental conditions increases progressively with the reduction in oxygen inspiratory pressure (PiO_2) (36) and is affected by subjects' fitness so that subjects with elevated maximal aerobic capacity are more affected by hypoxia (41).

The origin of exercise performance limitation in hypoxia is still under debate, since the consequences of reduced blood O_2 affect the whole organism. This limitation has been attributed to a lowered O_2 partial pressure in arterial blood (PaO_2) reducing arterial O_2 content and O_2 delivery to tissues with critical consequences on muscle metabolism and contraction (1, 46). Magnetic nerve stimulation has confirmed the effects of reduced arterial oxygenation on dynamic (12, 111) and static (54) exercise-induced alterations in muscle contractility. Reduced muscle O_2 delivery and exercise performance may result from impairments in pulmonary gas exchange (*e.g.* alveolar-capillary O_2 diffusion limitation (109)), reductions in maximal cardiac output and blood flow to locomotor muscles (17) and respiratory muscle fatigue (23) (for a review see (20)). Calbet et al. (17) demonstrated that the reduction in maximal oxygen consumption during cycling with an inspiratory O_2 fraction (FiO_2) of 0.105 was explained by the reduced PiO_2, impaired pulmonary gas exchange and reduced maximal cardiac output and leg blood flow, with each mechanism explaining approximately one-third of the reduction. These factors may, however, not entirely explain the hypoxia-induced reduction in exercise performance (57, 94, 115). Because biochemical, electromyographic (EMG) and mechanical signs of muscle fatigue at exhaustion are reduced in severe hypoxia compared to normoxia (*e.g.* (13, 56)), muscle metabolic fatigue may not be the main factor responsible for impaired whole-body exercise performance.

An alternative hypothesis is to consider the effects of hypoxia on the central nervous system (CNS) that may lead to altered central motor command and eventually reduced exercise performance (6). Neurons require continuous O_2 delivery in sufficient quantities to enable vital processes. The responsiveness of neurons to reduced O_2 availability is fast and they can immediately change their activities in response to hypoxia (29, 72). For example, severe hypoxia can affect cognitive performance (*e.g.* (59)). Some theories and indirect evidence suggest that the CNS may be sufficiently affected during exercise in hypoxia to become a limiting factor for exercise performance. In acute severe hypoxia, CNS alterations may precede the development of peripheral muscle fatigue and underlie the reductions in central motor output and exercise performance (13). This theory is supported by studies showing that hyperoxia at exhaustion quickly restores the ability of subjects to sustain the target workload and increases exercise performance in hypoxia (13, 17, 56, 101). Objective measurements of cerebral perfusion and oxygenation (3, 51, 81, 85, 91, 100, 101, 110) and supraspinal neuromuscular alterations (40, 86, 104, 105) have recently provided indications of brain adaptations to exercise in hypoxia. These results help to understand the mechanisms underlying the effects of hypoxia on central motor command and exercise performance.

This review addresses the main observations in humans regarding the impact of hypoxia on the brain during isolated and whole body exercise as well as questions that need to be addressed. Our approach includes the effects of changes in arterial oxygenation (and potential changes in arterial CO_2) on cerebral blood flow (CBF) and cerebral oxygenation, the impact of changes in cerebral oxygenation and its cellular consequences on neuron excitability and finally central drive to the muscles. We consider (i) the ‘direct effects’ of acute hypoxia on these different cerebral aspects during exercise, (ii) the potential ‘indirect effects' of acute hypoxia involving interactions between peripheral muscles and the CNS and (iii) the consequences of both direct and indirect effects on maximal voluntary activation and central motor command during submaximal and maximal exercise. The effects of chronic hypoxia (from several hours to several weeks) are also addressed.

DIRECT CEREBRAL EFFECTS OF ACUTE HYPOXIA

Cerebral blood flow

The majority of studies assessing changes in CBF during hypoxic exposure and exercise have used transcranial Doppler methods. This technique provides indirect evaluation of CBF from blood velocity in proximal intracranial or neck arteries. An important consideration is that, in addition to blood velocity, changes in diameter of insonated blood vessels could modulate CBF. The middle cerebral artery diameter (the most frequently measured) is nevertheless assumed to remain relatively constant with changes in blood gases and during exercise (4, 96), although recent data challenge this assumption in severe hypoxia (118).

Hypoxia at rest. Hypoxia *per se* is a cerebral vasodilator that increases CBF (24), at least beyond a certain threshold, *i.e.* arterial oxygen saturation (SpO_2) < 90% or PaO_2 < 40-45 mmHg (4). Hypoxic exposure at rest is associated with some degree of hyperventilation that results in hypocapnia. Since hypocapnia reduces CBF by vasoconstriction, changes in CBF result from the opposing effects of hypoxemia and hypocapnia (Fig. 1). Hence, little change in CBF is observed at rest when PaO_2 is reduced (5, 49, 74, 80), slight increases being possible as a function of the level of hypoxia and the amount of hyperventilation-induced hypocapnia. CBF can also be measured by arterial spin labeling (ASL) that magnetically tags blood water and measures its delivery to tissue capillaries, to obtain a global or regional measure of tissue perfusion.. When reducing FiO_2 from 0.21 to 0.12, ASL indicates increased whole-brain CBF (32) but no difference in the motor cortex (110), potentially due to regional specificity and/or insufficient signal-to-noise ratio.

Normoxic exercise. Consistent increases in middle cerebral artery blood velocity (MCAV) have been observed from rest to submaximal whole body normoxic exercise (50, 52, 62), whereas other cerebral arteries did not show a similar increase (55). Changes in CBF during exercise depend on cerebral areas being activated and are distributed heterogeneously within the brain (58), global CBF as measured with the Kety-Schmidt method remaining relatively constant from rest to maximal exercise (62). Note that regional CBF decreases near maximal-intensity exercise (39). Mechanisms thought to be involved in CBF regulation during exercise are cerebral autoregulation, *i.e.* the rapid response of cerebral blood vessels to changes in mean arterial pressure in order to keep CBF within physiologically tolerable limits, and CO_2 vasoreactivity. Thus, hyperventilation with concomitant reduction in arterial CO_2 partial pressure ($PaCO_2$) during intense exercise is a potential reason for reduced CBF when approaching maximal exercise (96).

Combined effects of hypoxia and exercise. Table 1 summarizes studies that have evaluated the effects of hypoxia on cerebral perfusion during exercise. While the vasodilator effect of hypoxia should accentuate the exercise-induced increase in CBF, reduced $PaCO_2$, due to hyperventilation during hypoxic exercise, probably blunts this effect and most studies reported similar blood velocity at submaximal or maximal exercise in normoxia and acute hypoxia (2, 49, 81, 101) (*e.g.* Fig. 1). Keeping end tidal CO_2 clamped during incremental exercise in acute hypoxia increases CBF but also reduces maximal performance (103). Although this result suggests that CBF is not a limiting factor at maximal exercise, clamping CO_2 also induces respiratory acidosis, increases ventilation and adverse respiratory sensations, potentially limiting exercise performance. Distinguishing the effect of reduced PaO_2 and $PaCO_2$ on hypoxic exercise CBF and performance remains therefore a challenge. In addition to the effect of changes in CO_2 on CBF, cerebral autoregulation may play a role since it is impaired during exercise in acute hypoxia (2). During finger tapping, Tuunanen and Kauppinen (110) reported a similar increase in motor cortex ASL signal intensity in hypoxia compared to normoxia, but over a smaller area of the parenchyma. Therefore, CBF during exercise is not enhanced when arterial oxygenation is reduced probably due to the vasoconstrictive effect of reduced $PaCO_2$. Some cerebral regions (including within the motor cortex (104)) may even undergo reduced perfusion potentially impairing O_2 delivery.

Cerebral oxygenation

NIRS is an optical method that noninvasively monitors regional changes in cerebral hemodynamics by measuring changes in attenuation of near-infrared light passing through tissue. NIRS is effective in assessing oxygenation changes in responses to brain activation including exercise (92, 100), utilizing the tight coupling between neuronal activity and regional CBF. Interpretation of cerebral NIRS measurements should however take into account the limited penetration depth of the light, potential perturbation from non-cerebral tissues (scalp and skull) and the fact that contributions of venous and arterial compartments to the signal cannot be distinguished. Contrary to muscle oxygenation which is maintained, cerebral oxygenation as measured with NIRS at rest is reduced in acute hypoxia (2, 51, 80, 91) suggesting a mismatch between O_2 delivery and O_2 utilization within the brain, at least in the brain regions under investigation (prefrontal cortex; *e.g.* Fig. 2). Interestingly, the increase in deoxyhemoglobin concentration did not correlate with changes in MCAV (80), indicating that changes in cerebral oxygenation and CBF at rest in hypoxia are, at least in part, distinct mechanisms.

In normoxia, prefrontal cortex oxygenation is increased during cycling whereas muscle oxygenation is reduced (92). Near maximal exercise however, cerebral oxygenation decreases (92), potentially because of an imbalance between a slight reduction in regional CBF and increased cerebral metabolic rate and O_2 uptake. Table 1 summarizes studies that have evaluated the effects of hypoxia on cerebral oxygenation during exercise. NIRS during exercise in hypoxia shows consistently reduced cerebral oxygenation both at submaximal (*e.g.* Fig. 2) and maximal intensities (2, 51, 81, 91, 93, 100-102). This reduction has been observed even in cases of enhanced CBF (51, 101) and no correlation was observed between changes in prefrontal oxygenation and MCAV during exercise (2). An elevated cerebral metabolic rate associated with greater O_2 consumption may explain this reduction in cerebral oxygenation during whole-body exercise in hypoxia (101). In hypoxia, whole body exercise and isolated contractions differ regarding cerebral oxygenation since the former accentuates cerebral deoxygenation (13, 100, 101) while the later is associated with some degree of cerebral reoxygenation (40, 91) compared to hypoxic resting levels. While most previous studies have only evaluated prefrontal oxygenation, Subudhi et al. (102) showed using multi-channel NIRS that cerebral oxygenation during hypoxic exercise is well correlated between the prefrontal, premotor and motor regions, although at maximal exercise deoxygenation of the prefrontal cortex was greater than in other regions.

Functional magnetic resonance imaging showed a linear increase in the blood-oxygen-level dependent (BOLD) signal (reflecting changes in blood oxygenation, blood flow and/or blood volume) of the sensorimotor cortex during graded activation of small muscle mass (finger tapping) (53). Liu et al. (60) reported during fatiguing submaximal constant-load handgrip contractions in normoxia a progressive increase in the BOLD signal which then reached a plateau toward the end of the task. This plateau - in line with the NIRS reduction in cerebral oxygenation near maximal exercise reported above (92) - can be interpreted as an altered central motor command, *i.e.* the so-called central fatigue. Such an interpretation should take into account that modified BOLD signals can reflect changes in neuronal input and/or processing and changes in inhibitory and/or excitatory inputs (84). In some parts of the cortex involved in motor task performance in normoxia (supplementary motor areas, the supramarginal gyrus and parts of the motor cortex), BOLD changes during finger tapping are strongly attenuated by hypoxia, further suggesting that hypoxia may not uniformly affect all brain regions (110). Techniques allowing regional assessment of cerebral perfusion and oxygenation (such as MRI and multi-channel NIRS) will be helpful in better describing the topographic localization of cerebral perturbations associated with isolated and whole body exercise in hypoxia.

Brain mitochondrial oxygen tension and cerebral metabolism

Mitochondrial oxygen tension ($PmitoO_2$) and brain's metabolic response to exercise can be estimated from the arterio-venous differences and CBF (25, 85). It has been speculated that a reduction in $PmitoO_2$ of more than 6-7 mmHg (no absolute $PmitoO_2$ can be measured with this method), due to reduced arterial oxygenation and/or CBF, may be associated with impaired cerebral aerobic metabolism (85). Strenuous exercise in normoxia could induce a drop in $PmitoO_2$ remaining slightly below this threshold (39). When exercise is performed under acute hypoxic conditions, the reduction in $PmitoO_2$ may be exacerbated due to the combination of reduced arterial O_2 delivery and unchanged maximal O_2 extraction fraction (75). Rasmussen et al. (86) confirmed that $PmitoO_2$ during intense cycling in hypoxia is further reduced (-11 mmHg) compared to cycling in normoxia both at the same absolute workload (+3 mmHg) and at maximal intensity (-8 mmHg), thus potentially impairing cerebral mitochondrial ATP production.

Brain metabolism during exercise has been expressed as the cerebral metabolic ratio of O_2 *vs.* substrates ($MR = CMRO_2 / CMR_{glucose + ½ lactate}$) (25). During intense exercise in normoxia, $CMR_{glucose+lactate}$ increases out of proportion to $CMRO_2$, thereby reducing MR (39, 114), possibly due to the role of glycolysis and lactate in fueling neuronal activity (25). Rasmussen et al. (86) reported reduced $CMRO_2$ during intense whole body exercise in hypoxia compared to low (*i.e.* at same absolute workload) or maximal intensity exercise in normoxia. A greater reduction in MR from rest to exercise was found in hypoxia compared to normoxia at the same absolute workloads, while the MR reduction was similar for comparable relative workloads. Similar results were reported by Volianitis et al. (114), *i.e.* comparable reductions in MR during 2000-m all-out rows performed with FiO_2 of 0.17, 0.21 and 0.30. This finding suggests that hypoxia alters MR for a given absolute work output (possibly due to greater cerebral activation in order to increase central drive to cope with larger muscle fatigue) but not at similar relative intensities.

Rasmussen et al. (86) showed net cerebral lactate uptake during intense exercise in normoxia but not in hypoxia despite similar arterial lactate concentrations. Volianitis et al. (114) also reported significantly reduced arterio-jugular venous lactate differences during intense exercise in hypoxia compared to normoxia. This suggests a modified balance between brain lactate uptake and release during intense exercise in hypoxia, with reduced lactate uptake and/or greater lactate release compared to normoxia (75). The potential role of the hypoxia-induced changes in brain lactate exchange and metabolism on neuronal function in the context of central fatigue remains to be elucidated.

Effect of cerebral oxygenation on exercise performance: lessons from hyperoxia

To determine to what extent the reduction in cerebral oxygenation can impair exercise performance, some studies have evaluated the effect of increasing FiO_2 during whole-body exercise on cerebral oxygenation and performance (13, 81, 101). Subudhi et al. (101) increased surreptitiously FiO_2 to 0.60 at $\dot{W}_{max}$ of incremental cycling tests performed in normoxia and hypoxia (PiO_2 = 86 Torr, ~4300 m). Hyperoxia increased cycling time in hypoxia only and improved both cerebral and locomotor muscle oxygenation assessed by NIRS over the frontal lobe and *vastus lateralis*, respectively (Fig. 3). Similarly, Peltonen et al. (81) reported improved performance with enhanced cerebral and muscle perfusion when subjects were switched to hyperoxia at the end of a maximal incremental cycling test in hypoxia (PiO_2 = 118 mmHg, ~2500 m). In both studies, the greater effect of switching to hyperoxia was observed on cerebral oxygenation compared to muscle oxygenation (Fig. 3). Peltonen et al. (81) suggested that tissue-specific control mechanisms may underlie differences between cerebral and muscle tissues regarding hypoxia-induced perfusion and oxygenation changes although the mechanisms responsible for such differences remain to be elucidated. Because of the simultaneous and rapid effect of hyperoxia at exhaustion on cerebral oxygenation and exercise tolerance, cerebral deoxygenation is thought to be an important factor underlying exercise performance limitation in hypoxia (6). However, a potential role of mechanisms other than cerebral re-oxygenation inducing increased exercise performance in hyperoxia cannot be ruled out (*e.g.* cardiovascular changes). The effect of low brain oxygenation (and re-oxygenation) on performance during other types of exercise protocols limiting the influence of large cardiovascular changes (*e.g.* prolonged submaximal whole-body exercise or isolated muscle exercise) needs to be investigated.

Cortex excitability

Transcranial magnetic stimulation (TMS) is a noninvasive technique that allows stimulation of small brain areas. Stimulation of the motor cortex can evoke short-latency excitatory EMG (motor-evoked potential, MEP) and mechanical (twitch) responses in many muscles. When TMS is delivered during a voluntary contraction, MEPs are followed by a period of EMG silence called the cortical silent period (CSP) reflecting intracortical inhibition. During fatiguing muscle contractions in normoxia, increased MEP amplitude (reflecting greater corticospinal excitability) and CSP lengthening (reflecting greater intracortical inhibition) are observed (37).

In acute severe hypoxia at rest (20-30 min with FiO_2 = 0.12, SpO_2 ~75%), Szubski et al. (104) showed unchanged MEP amplitudes, a reduced resting motor threshold (RMT) and shorter CSP compared to normoxia, suggesting that acute hypoxia may increase cortical excitability and decrease intracortical inhibition. Conversely, after 10-min wash-in periods at rest with various gas mixtures (FiO_2 = 0.10-0.21), Goodall et al. (40) reported that corticospinal excitability and inhibition were similar in hypoxia and normoxia. Differences between studies regarding the effects of hypoxia at rest on corticospinal excitability may arise from differences in the muscle group tested (first dorsal interosseous *vs.* quadriceps muscles) or the length of exposure to hypoxia. Regarding the latter, the effect of hypoxemia on cerebral tissue oxygenation has relatively prolonged kinetics, *i.e.* 10-20 min of hypoxic breathing may be insufficient to reach a cerebral deoxygenation steady state (*e.g.* Fig. 2, or Fig. 3 in ref. (40)). Therefore, a more prolonged wash-in period with the hypoxic gas (>30 min to reach steady state cerebral oxygenation, personal data) should be used in order to observe the effect of acute hypoxia on neuronal excitability. Szubski et al. (105) reported after a 90-s maximal voluntary contraction (MVC) of the first dorsal interosseus muscle that MEP amplitude increased and CSP decreased to a similar extent in normoxia and hypoxia, indicating similar responses in corticospinal excitability and intracortical inhibition. Millet et al. (67) observed no difference in MEP or CSP between normoxia or hypoxia (FiO_2 = 0.09-0.14) during intermittent isometric submaximal (40% MVC) contractions of the elbow flexors under vascular occlusion. Goodall et al. (40) found no change in corticospinal excitability during exercise using TMS on the knee extensors before or after intermittent isometric submaximal (60% MVC) leg extensions to task failure in normoxia or hypoxia (FiO_2 = 0.10-0.16). Based on these studies (40, 67, 104, 105), hypoxia may change corticospinal excitability at rest while, during fatiguing exercise with small muscle mass, it does not impair the responsiveness of neurons involved in central motor drive to a greater extent than normoxia.

Arguments in favor of hypoxia-induced perturbations of cerebral neuron activity also come from electroencephalographic recordings indicating reduced activity in hypoxia compared to normoxia both at rest (78) and during mental tasks (79). Animal and *in vitro* studies suggest that alterations in CNS neurotransmitter turnover (*e.g.* acetylcholine, dopamine, norepinephrine and serotonin (38, 77)), ion homeostasis and channel activity (reduced ion channel and pump activity (42, 73)) might underlie hypoxia-induced changes in brain neuronal excitability.

INDIRECT CEREBRAL EFFECTS OF ACUTE HYPOXIA

Afferent signals from working muscles

Sensory feedback from the fatigued locomotor muscles to the CNS may be a determinant of central motor drive and therefore exercise performance. This hypothesis is supported by both the increased motor drive during the first half of a normoxic 5-km cycling time trial performed with impaired cortical projection of opioid-mediated muscle afferents by intrathecal fentanyl injection and the excessive development of locomotor muscle fatigue observed over the course of the time-trial (11). Spinal opioid receptor muscle afferents may influence cerebral adaptations to exercise by facilitating intracortical inhibition (45). Consequently, under moderate hypoxic conditions, muscle fatigue may represent a key factor responsible for impaired central drive in hypoxia through enhanced muscle inhibitory afferent signals because of an accelerated development of locomotor muscle fatigue (12, 54). This statement is supported by the parallel hypoxia-induced (F_IO_2 = 0.15) reductions in integrated EMG (iEMG) and power output during a 5-km cycling time trial, while peripheral muscle fatigue at exhaustion does not differ (7). Discharge of group III/IV afferents in cats is higher during muscle contractions in hypoxia compared to normoxia, as a consequence of both a higher baseline firing frequency and an additional increase during exercise triggered by hypoxia-induced accumulation of muscle metabolites (44). Increased activity of peripheral muscle afferents in hypoxia (44) could alter brain activity as suggested from recordings of electroencephalographic activity in a cat model (14). Therefore, in addition to CNS hypoxia *per se*, the effect of hypoxia on central motor drive may also involve changes in afferent signals from both locomotor and respiratory muscles (facing an increased work of breathing (23, 111)) to the CNS. These mechanisms may be critical up to an acute level of SpO_2 >70%, whereas below this level the aforementioned direct effects of hypoxia on cerebral function appear to dominate the regulation of muscular performance (6, 13). While blockade of neural feedback from working muscles with epidural anesthesia does not impair hypoxia-induced increases in systemic cardiovascular and neuroendocrine responses (57), evaluation of the central motor drive during hypoxic exercise when manipulating muscle afferent signals is needed to confirm their impact on the CNS in hypoxic conditions. This should include selective blockade of ascending sensory pathways and avoid the confounding effect of motor nerve activity or maximal force output impairments (10, 11, 57).

Concurrence for blood flow

A plateau or slight reduction in CBF near maximal exercise in normoxia has been suggested to be due to (i) competition for blood flow between working muscles and the brain and/or (ii) a plateau or decline in cardiac output (47, 90). Also, respiratory muscle work during normoxic exercise can reduce blood flow to the locomotor muscle, enhance locomotor muscle fatigue and impair exercise performance (43, 89). By changing FiO_2 and/or the work of breathing (by using pressure-assisted ventilation) during exercise, it has been demonstrated that the increased work of breathing during hypoxic exercise independently enhances locomotor muscle fatigue during cycling, probably by reducing blood flow to the legs (9). Given these results, it can be hypothesized that brain perfusion during high-intensity hypoxic exercise might be compromised by (i) competition for blood flow distribution in face of increased locomotor muscle perfusion compensating for reduced arterial oxygenation (17), and (ii) the increased work of breathing potentially impairing blood flow to other regions of the body (9). In support, greater alteration in brain *vs.* muscle oxygenation (as determined by NIRS) in hypoxia compared to normoxia was reported during rest and exercise (2, 102), leading the authors to suggest that a "steal" of blood from cerebral circulation to the muscle may occur in hypoxia. The potential competition for blood flow between the brain and other parts of the body during hypoxic exercise remains to be specifically investigated.

CONSEQUENCES OF ACUTE HYPOXIA ON MOTOR DRIVE

Voluntary activation

Peripheral nerve stimulation. The central component of neuromuscular function can be assessed from the level of maximal voluntary activation (VA). VA is measured with peripheral nerve stimulation and the twitch interpolation technique, leading to the definition of central fatigue as an activity-induced decline in the ability to activate a muscle voluntarily (37). In normoxia, reductions in VA have been reported following isolated muscle contractions (107) and whole-body exercise (65).

Goodall et al. (40) and Romer et al. (87) observed significant reductions in VA after exhaustive normoxic exercise and compared these alterations in central motor drive in hypoxic conditions. Goodall et al. (40) observed no difference in VA reduction (estimated by femoral nerve stimulation) at task failure following isometric submaximal knee extensions between normoxic and hypoxic (FiO_2 = 0.10-0.16) conditions, but VA was not assessed for the same exercise duration. Romer et al. (87) measured VA before and after constant-load cycling at 92% of normoxic $\dot{W}_{max}$ in normoxia and hypoxia (FiO_2 = 0.13); the reduction in VA observed at exhaustion in hypoxia was only slightly greater than in normoxia for the same exercise duration (-10 *vs.* -5%, P = 0.11), while similar to the reduction observed at exhaustion in normoxia. In endurance athletes at sea level, preventing exercise-induced hypoxemia (SpO_2 = 92% on average) by increasing FiO_2 from 0.21 to 0.27 reduces locomotor muscle contractile fatigue and also post-exercise reduction in VA (88), indicating that even slight hypoxemia can exacerbate exercise-induced activation deficit. These data suggest a greater impairment in the ability of the CNS to maximally activate muscles following a given fatiguing exercise performed in hypoxia compared to normoxia, potentially contributing to exercise performance impairment. This reduced central drive could be due to an effect of hypoxia on alpha motoneuronal responsiveness, but alpha motoneurons are relatively insensitive to hypoxia (33). It is also unlikely that the reduced VA can be attributed to alteration of the peripheral nerves since hyperexcitability has been reported in peripheral nerves (117). Reduced Hoffmann reflex responses in acute (20 min) hypoxia at rest suggested an inhibitory effect on the spinal motoneurons via descending influences (117), but this was not confirmed in another study (27) and definitive conclusions cannot be made.

The fact that all results do not confirm a greater VA reduction following hypoxic exercise may be due to limitations of this variable to detect central fatigue (37) including (i) the task specificity of VA (*i.e.* VA is measured during isometric MVC while whole-body exercise performance involves repetitive submaximal contractions), (ii) its inability to distinguish spinal and supraspinal factors, (iii) the delay between the end of exercise (*e.g.* cycling) and the time VA is measured on a dedicated ergometer (*e.g.* quadriceps chair) and (iv) non-linearity of the voluntary force-VA relationship.

Cortical stimulation. Maximal voluntary activation can also be evaluated with TMS during submaximal and maximal voluntary contractions (108), *i.e.* providing assessment of cortical VA. During fatiguing muscle contractions in normoxia, cortical VA is reduced (108), confirming that part of neuromuscular fatigue in some normoxic conditions (*e.g.* during sustained submaximal isometric elbow flexion (98)) can be attributed to suboptimal drive from the motor cortex (37). Szubski et al. (105) and Goodall et al. (40) assessed cortical VA following a fatiguing exercise in hypoxia. Following a 90-s MVC of the first interosseus muscle, Szubski et al. (105) reported similar reductions in normoxia and hypoxia in the force increment evoked by TMS during MVC expressed as the percentage of the mean voluntary force immediately before the stimulation. In the study of Goodall et al. (40), short term (10 min) hypoxic exposure at rest did not impair cortical VA. Only severe hypoxia (FiO_2 = 0.10) reduced the time to task failure during intermittent isometric submaximal leg extensions compared to normoxia (from 24.7 ± 5.5 to 15.9 ± 5.4 min) and induced a distinct pattern of fatigue compared to the other conditions. While quadriceps contractile fatigue at task failure was attenuated compared to normoxia, the reduction in cortical VA was greater (Fig. 4), being responsible for more than half the decrease in maximal voluntary strength. Also, a correlation (r = 0.93) for group mean values between post-exercise cortical VA and cerebral oxygenation (assessed by NIRS) was observed. This study indicates that reduced cerebral oxygenation and subsequent alterations in central drive play a key role in isolated muscle exercise limitation in acute severe hypoxia (contrary to moderate hypoxia (105)).

One study (86) has evaluated the relationship between brain metabolism and cortical VA during whole-body exercise in hypoxia. During intense cycling in hypoxia (FiO_2 = 0.10) and low (*i.e.* at the same absolute workloads) and maximal intensity cycling in normoxia (FiO_2 = 0.21), cortical VA of the elbow flexor muscles (*i.e.* a muscle group not involved in cycling) was measured with TMS. While low intensity exercise in normoxia did not modify maximal elbow flexor strength and cortical VA, cycling in hypoxia at the same absolute power output and maximal cycling in normoxia reduced maximal elbow flexor strength and cortical VA. Since no signs of contractile fatigue of the elbow flexors in response to muscle electrical stimulation were observed in any condition, the fatigue in hypoxia and during maximal exercise in normoxia was attributed to central origin. These results suggest that inadequate oxygenation of the brain and subsequent perturbation of cerebral metabolism may underpin central fatigue and the reduction in VA. Concomitant measurement of brain oxygenation and metabolism and cortical VA of the muscle mass involved in a fatiguing exercise is needed to better evaluate the impact of cerebral alterations on performance.

Central motor command

Central motor command can be evaluated from EMG signals measured during muscle contractions. Although EMG evaluations are frequently used, important limitations should be taken into account regarding interpretations with fatigue (30). EMG responses can give an insight into central motor drive during voluntary contractions, provided this variable is normalized to the maximal M-wave, *i.e.* the EMG response to a single supramaximal stimulus, especially during fatigue studies (66). The reduction in $\dot{W}_{max}$ during whole body exercise in hypoxia complicates the comparison between normoxic and hypoxic conditions since for a given absolute workload the relative intensity, and therefore the cardio-respiratory and muscular constraints, is higher in hypoxia. Isolated exercise protocols involving a small muscle mass have the advantage of being carried out at the same relative intensity in normoxia and hypoxia since acute hypoxia has no effect on MVC (83), and does not involve the cardiorespiratory system to a great extent (21). Table 2 summarizes studies using surface EMG signals to assess the effect of hypoxia on central motor drive during exercise and at exhaustion.

EMG responses to isolated exercise. During intermittent submaximal contractions of the knee extensors, Fulco et al. (35) and Katayama et al. (54) showed that acute hypoxia (PiO_2 = 464 Torr and FiO_2 = 0.11, respectively) accelerates the increase in iEMG from the beginning to the end of exercise. This increase in iEMG is interpreted as an increase in motor command in order to recruit additional motor units and/or to increase motoneuron discharge rate to compensate for contractile failure in active muscle fibers. Since contractile fatigue is enhanced during leg extensions in hypoxia (54), the greater increase in iEMG during submaximal contractions in hypoxia may illustrate an increased motor command compensating for the development of contractile fatigue (40). This increase in EMG during isolated submaximal contractions in hypoxia was not observed in other studies that reported similar EMG changes during sustained submaximal (55) or maximal (31) muscle contractions in hypoxia and normoxia. During sustained contractions (26, 31, 55), high intramuscular pressure causes substantial ischemia (both in normoxia and hypoxia) that may induce comparable contractile failure and therefore similar increase in EMG and central motor drive in normoxia and hypoxia (55).

In order to separate the central and peripheral effects of hypoxia, including the potential inhibitory effect of sensory feedback from working muscles, Millet et al. (64) induced ischemia of the exercising muscles, therefore maintaining a similar metabolic state within the working muscle independent of changes in FiO_2. Subjects performed an intermittent isometric knee extension protocol (at 50% MVC) in normoxia or hypoxia (FiO_2 = 0.11), with or without leg circulation occlusion (with a 250 mmHg cuff inflated proximally on the thigh). No effect of hypoxia on the rate of increase in EMG root mean square (RMS) of the knee extensors during exercise with the cuff inflated was observed. Similar stimulation of muscle afferents with leg circulation occlusion may explain this result and therefore supports a link between changes in central drive and afferent signals during hypoxic exercise. The maximum number of knee extensions with the cuff on was reduced during hypoxia compared to normoxia (8.2 ± 2.6 *vs.* 9.4 ± 3.1 repetitions), suggesting a specific though modest effect of CNS hypoxia on performance. In a recent study, Millet et al. (67) evaluated the effect of more severe hypoxia (FiO_2 = 0.09) in a similar setting for the elbow flexors. They showed a significant, yet modest, performance reduction with circulation occlusion in severe *versus* moderate hypoxia and normoxia while peripheral muscle fatigue and oxygenation (NIRS) were similar in all three conditions, further demonstrating the direct cerebral effect of severe hypoxia, at least during such isolated muscle exercise.

EMG responses to whole-body exercise. When comparing iEMG during cycling at the same absolute workload in normoxia and hypoxia, greater iEMG increases for the same exercise duration have been reported in hypoxia (12, 13, 106), similar to the results during leg extensions. Therefore, during submaximal whole-body exercise in acute hypoxia, the CNS is able to increase motor drive above levels observed in normoxia to sustain the workload in order to compensate for increased levels of contractile fatigue (87). The severity of hypoxia plays a critical role regarding the ability of the CNS to increase motor drive during exercise. Amann et al. (13) showed that in severe (FiO_2 = 0.10) but not moderate (FiO_2 = 0.15) hypoxia, the iEMG increment during intense constant-load cycling is reduced compared to normoxia, while hyperoxia at exhaustion prolonged exercise duration with a concomitant increase in iEMG (Fig. 5). Thus, in acute severe hypoxia, cerebral alterations due to hypoxia may precede the development of peripheral muscle fatigue ((13), Fig. 5) and lead to reduced central drive and muscle power output. Whether under such conditions (*i.e.* whole-body exercise in severe hypoxia) impaired neuronal excitability is one of the mechanisms underlying the reduced central drive remains to be investigated.

EMG during maximal voluntary contractions. MVC can either be sustained or performed repeatedly before and after submaximal contractions in order to assess the development of fatigue. During MVC without fatigue, acute hypoxia has no effect on maximal EMG, in accordance with unchanged maximal voluntary strength (83). When comparing the evolution of maximal iEMG during MVC after submaximal contractions at the same absolute intensity, similar (after 3 sets of isometric leg extensions (54) and after 10 min of cycling (106)) or greater (after dynamic leg extensions to exhaustion (35)) reductions in MVC iEMG have been reported in hypoxia compared to normoxia. A greater reduction in MVC iEMG may reflect some alterations in central neural pathways, partly explaining the greater reduction in MVC observed under hypoxic conditions (35). However, as explained above, one cannot interpret changes in EMG during MVC as alterations of the central motor drive only because of amplitude cancellation (30) and potential alterations at the spinal, neuromuscular junction or sarcolemmal levels. In this context, EMG or mechanical responses to electrical and/or magnetic stimulation are needed to better understand how hypoxia affects maximal activation of motor units.

Rasmussen et al. (85) evaluated the effect of inhaling gas mixtures with FiO_2 from 0.10 to 1.0 and concomitant changes in brain oxygenation on motor performance evaluated by maximum handgrip strength. Stepwise forward-regression analysis showed that the best predictor of maximal handgrip strength was cerebral oxygenation measured by NIRS. However, the impact of cerebral oxygenation on maximal motor drive remains to be confirmed since such a reduction in maximal voluntary strength is not a universal finding (83).

EFFECTS OF CHRONIC HYPOXIA

Over the first hours of hypoxic exposure, minor changes in CBF have been observed (48, 74, 99), depending on hyperventilation-induced hypocapnia (74) and the level of hypoxia. With more prolonged hypoxia (several days), CBF at rest returns to values observed in normoxic conditions (48, 61, 71), probably due to the combination of changes in blood gases, cerebrovascular reactivity and cerebrospinal fluid acid-base status with acclimatization (16, 61, 97). Compared to normoxia, increased MCAV during exercise has been reported in chronic hypoxia (51, 101), but whether this change is different from that in acute hypoxia is uncertain (48, 101). On one hand, smaller increase in CBF during exercise with chronic exposure to low PaO_2 may be due to (i) improved arterial oxygenation with acclimatization making the increase in flow to preserve brain O_2 supply unnecessary, and (ii) greater hyperventilation-induced hypocapnia after acclimatization that may blunt the increase in CBF during exercise (49). On the other hand, the reduction in cerebrovascular reactivity to CO_2 with acclimatization may attenuate the hypocapnic-mediated reduction in CBF (101).

Cerebral deoxygenation measured by NIRS is greater at the same absolute work load and at maximal exercise during chronic *vs.* acute hypoxia (4300 m), while muscle oxygenation is unchanged (101). The authors suggested that this greater cerebral deoxygenation is due to the combined effect of differences in cerebrovascular responses and elevated cerebral metabolic rates. Insufficient brain oxygenation may still contribute to performance limitation during maximal exercise despite acclimatization to high altitude since acute reoxygenation at peak exercise during chronic severe hypoxia (5050-5260 m) enables subjects to continue exercise and increase their maximal workloads (18, 56).

Evaluation of motor cortex excitability by TMS after 3-5 days at 4554 m (SpO_2 ~84%) suggests a hypoexcitability of both the excitatory and inhibitory cortical circuits, with higher RMT and lower short-interval intracortical inhibition (SICI) as well as tendencies towards lower MEP and intracortical facilitation compared to normoxia (68). The severity of acute mountain sickness and SpO_2 at altitude correlated with the changes in RMT and SICI, respectively. Thus, cerebral alterations associated with hypoxic exercise may show inter-individual differences analogous to acute mountain sickness sensitivity, although the underlying mechanisms may differ (99). Changes in cortical excitability observed in hypoxemic patients with chronic respiratory insufficiency further suggest that chronic hypoxia can induce alterations in cerebral neuronal excitability (70, 76). In patients suffering from chronic obstructive pulmonary disease, motor threshold is increased (70) and MEP is unchanged (70, 76). The effect on CSP is controversial (70, 76). Moreover, motor cortex adaptations observed in chronic obstructive pulmonary disease patients were reversed by 3 months of oxygen therapy (76), supporting that the observed cortical changes were induced by hypoxia. Since hypoxemia can alter the synaptic inhibitory γ-aminobutyric acid (GABAergic) transmission (69) that underlies intracortical inhibition and CSP (116), the cortical effect of chronic hypoxia may be associated with GABAergic dysfunction (8, 76) although other mechanisms may also be involved (73).

Similar to acute hypoxia, no significant change in MVC are observed in chronic hypoxia (83). Conversely, the increase in EMG signal during isolated submaximal contractions reported in acute hypoxia was not observed after 1 month at 5050 m by Kayser et al. (56), who reported similar iEMG changes during intermittent submaximal forearm exercise compared to normoxia. Esposito et al. (34) also reported similar reductions in EMG RMS during a 1-min MVC of knee or elbow extensors performed at sea level and after 43 days at 5050 m. Changes associated with acclimatization (*e.g.* myoelectrical alterations, muscle structural and/or metabolic adaptations (22)) may explain why changes in EMG observed in acute hypoxia compared to normoxia are not observed anymore in chronic hypoxia. Conversely, during cycling exercise at sea level or at altitude $\dot{W}_{max}$, Kayser et al. (56) observed a smaller rise in quadriceps iEMG in chronic hypoxia compared to normoxia both for the same exercise duration and at exhaustion. The authors suggested that central drive might be limited in hypoxia during exercise involving a large as opposed to small muscle mass and that performance limitation may be centrally mediated during this type of exercise. The difference between studies having observed greater iEMG signals in acute hypoxia (12, 13, 106) and the study by Kayser et al. (56) may arise from (i) differences in characteristics of the hypoxic stress, *i.e.* chronic and severe hypobaric hypoxia in Kayser's study (1 month at 5050 m) *vs.* acute moderate normobaric hypoxia in the other experiments (FiO_2 = 0.12 or 0.15) and (ii) differences in exercise intensity (local $\dot{W}_{max}$ in Kayser's study *vs.* the same submaximal absolute workload in the other studies). To better understand the cerebral effects of chronic hypoxia, its impact on VA both in unfatigued and fatigued states remains to be investigated. Only one study in chronically hypoxemic patients reported reduced VA compared to age-matched healthy controls (113).

The effect of hypoxia on the brain can also be observed in terms of anatomy. Several hours of hypoxia is able to modify brain volume by inducing edema (95) while several days or weeks at high altitude may be associated with changes in brain morphology, including the motor cortex (28). Whether these changes associated with chronic hypoxia lead to changes in cerebral responses to exercise is unknown.

CONCLUSION

Several aspects of cerebral function are impaired during hypoxic exercise compared to either normoxic exercise or hypoxia at rest, indicating that the CNS is important for exercise performance limitation in hypoxia. Impaired cerebral perfusion and/or oxygenation during hypoxic exercise can underpin reduced central drive to the locomotor muscles although the intermediate neuronal mechanisms remain to be elucidated (Fig. 6). The integration of the different cerebral alterations observed during hypoxic exercise (perfusion, oxygenation, metabolism, neuronal excitability and electrical activity) is required and would benefit from a combination of methodologies offering complementary insights into the brain in hypoxia. Besides the direct cerebral effects of hypoxia that are believed to mostly play a major role in severe hypoxia, afferent signals from working muscles to the CNS appear to be important for reduced central drive during hypoxic exercise (Fig. 6). In addition to seeking neuronal cellular mechanisms and a more integrated view of cerebral alterations during hypoxic exercise, research should consider (i) potential inter-individual differences regarding cerebral alterations associated with hypoxic exercise, analogous to the sensitivity to acute mountain sickness and (ii) the interconnection of the cerebral alterations with psychomotor (*e.g.* decision-making) and cognitive factors since they may participate to exercise performance limitation and share common cerebral mechanisms (63, 112).

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Perspectives and significance:

Impairment of several aspects of the cerebral function has been demonstrated during hypoxic exercise, suggesting that the brain may be a critical factor underlying exercise performance limitation under this condition. Further studies are needed to provide a more integrated view of the impact of hypoxemia on the brain from cerebral blood flow to central motor command. This will be of value for a better understanding of exercise limitation at altitude but also relevant for exercise response in hypoxemic patients.

REFERENCES

1. **Adams RP, and Welch HG**. Oxygen uptake, acid-base status, and performance with varied inspired oxygen fractions. *J Appl Physiol* 49: 863-868, 1980.

2. **Ainslie PN, Barach A, Murrell C, Hamlin M, Hellemans J, and Ogoh S**. Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: rest and exercise. *Am J Physiol Heart Circ Physiol* 292: H976-983, 2007.

3. **Ainslie PN, Hamlin M, Hellemans J, Rasmussen P, and Ogoh S**. Cerebral hypoperfusion during hypoxic exercise following two different hypoxic exposures: independence from changes in dynamic autoregulation and reactivity. *Am J Physiol Regul Integr Comp Physiol* 295: R1613-1622, 2008.

4. **Ainslie PN, and Ogoh S**. Regulation of cerebral blood flow in mammals during chronic hypoxia: a matter of balance. *Exp Physiol* 95: 251-262, 2009.

5. **Ainslie PN, and Poulin MJ**. Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide. *J Appl Physiol* 97: 149-159, 2004.

6. **Amann M, and Calbet JA**. Convective oxygen transport and fatigue. *J Appl Physiol* 104: 861-870, 2008.

7. **Amann M, Eldridge MW, Lovering AT, Stickland MK, Pegelow DF, and Dempsey JA**. Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. *J Physiol* 575: 937-952, 2006.

8. **Amann M, and Kayser B**. Nervous system function during exercise in hypoxia. *High Alt Med Biol* 10: 149-164, 2009.

9. **Amann M, Pegelow DF, Jacques AJ, and Dempsey JA**. Inspiratory muscle work in acute hypoxia influences locomotor muscle fatigue and exercise performance of healthy humans. *Am J Physiol Regul Integr Comp Physiol* 293: R2036-2045, 2007.

10. **Amann M, Proctor LT, Sebranek JJ, Eldridge MW, Pegelow DF, and Dempsey JA**. Somatosensory feedback from the limbs exerts inhibitory influences on central neural drive during whole body endurance exercise. *J Appl Physiol* 105: 1714-1724, 2008.

11. **Amann M, Proctor LT, Sebranek JJ, Pegelow DF, and Dempsey JA**. Opioid-mediated muscle afferents inhibit central motor drive and limit peripheral muscle fatigue development in humans. *J Physiol* 587: 271-283, 2009.

12. **Amann M, Romer LM, Pegelow DF, Jacques AJ, Hess CJ, and Dempsey JA**. Effects of arterial oxygen content on peripheral locomotor muscle fatigue. *J Appl Physiol* 101: 119-127, 2006.

13. **Amann M, Romer LM, Subudhi AW, Pegelow DF, and Dempsey JA**. Severity of arterial hypoxaemia affects the relative contributions of peripheral muscle fatigue to exercise performance in healthy humans. *J Physiol* 581: 389-403, 2007.

14. **Balzamo E, Lagier-Tessonnier F, and Jammes Y**. Fatigue-induced changes in diaphragmatic afferents and cortical activity in the cat. *Respir Physiol* 90: 213-226, 1992.

15. **Bendahan D, Badier M, Jammes Y, Confort-Gouny S, Salvan AM, Guillot C, and Cozzone PJ**. Metabolic and myoelectrical effects of acute hypoxaemia during isometric contraction of forearm muscles in humans: a combined 31P-magnetic resonance spectroscopy-surface electromyogram (MRS-SEMG) study. *Clin Sci (Lond)* 94: 279-286, 1998.

16. **Brugniaux JV, Hodges AN, Hanly PJ, and Poulin MJ**. Cerebrovascular responses to altitude. *Respir Physiol Neurobiol* 158: 212-223, 2007.

17. **Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B**. Determinants of maximal oxygen uptake in severe acute hypoxia. *Am J Physiol Regul Integr Comp Physiol* 284: R291-303, 2003.

18. **Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, and Saltin B**. Why is VO2 max after altitude acclimatization still reduced despite normalization of arterial O2 content? *Am J Physiol Regul Integr Comp Physiol* 284: R304-316, 2003.

19. **Calbet JA, De Paz JA, Garatachea N, Cabeza de Vaca S, and Chavarren J**. Anaerobic energy provision does not limit Wingate exercise performance in endurance-trained cyclists. *J Appl Physiol* 94: 668-676, 2003.

20. **Calbet JA, and Lundby C**. Air to muscle O2 delivery during exercise at altitude. *High Alt Med Biol* 10: 123-134, 2009.

21. **Calbet JA, Radegran G, Boushel R, and Saltin B**. On the mechanisms that limit oxygen uptake during exercise in acute and chronic hypoxia: role of muscle mass. *J Physiol* 587: 477-490, 2009.

22. **Caquelard F, Burnet H, Tagliarini F, Cauchy E, Richalet JP, and Jammes Y**. Effects of prolonged hypobaric hypoxia on human skeletal muscle function and electromyographic events. *Clin Sci (Lond)* 98: 329-337, 2000.

23. **Cibella F, Cuttitta G, Kayser B, Narici M, Romano S, and Saibene F**. Respiratory mechanics during exhaustive submaximal exercise at high altitude in healthy humans. *J Physiol* 494 (Pt 3): 881-890, 1996.

24. **Cohen PJ, Alexander SC, Smith TC, Reivich M, and Wollman H**. Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in conscious man. *J Appl Physiol* 23: 183-189, 1967.

25. **Dalsgaard MK**. Fuelling cerebral activity in exercising man. *J Cereb Blood Flow Metab* 26: 731-750, 2006.

26. **Degens H, Sanchez Horneros JM, and Hopman MT**. Acute hypoxia limits endurance but does not affect muscle contractile properties. *Muscle Nerve* 33: 532-537, 2006.

27. **Delliaux S, and Jammes Y**. Effects of hypoxia on muscle response to tendon vibration in humans. *Muscle Nerve* 34: 754-761, 2006.

28. **Di Paola M, Bozzali M, Fadda L, Musicco M, Sabatini U, and Caltagirone C**. Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. *Eur J Neurol* 15: 1050-1057, 2008.

29. **Dillon GH, and Waldrop TG**. In vitro responses of caudal hypothalamic neurons to hypoxia and hypercapnia. *Neuroscience* 51: 941-950, 1992.

30. **Dimitrova NA, and Dimitrov GV**. Interpretation of EMG changes with fatigue: facts, pitfalls, and fallacies. *J Electromyogr Kinesiol* 13: 13-36, 2003.

31. **Dousset E, Steinberg JG, Balon N, and Jammes Y**. Effects of acute hypoxemia on force and surface EMG during sustained handgrip. *Muscle Nerve* 24: 364-371, 2001.

32. **Dyer EA, Hopkins SR, Perthen JE, Buxton RB, and Dubowitz DJ**. Regional cerebral blood flow during acute hypoxia in individuals susceptible to acute mountain sickness. *Respir Physiol Neurobiol* 160: 267-276, 2008.

33. **Eccles RM, Loyning Y, and Oshima T**. Effects of hypoxia on the monosynaptic reflex pathway in the cat spinal cord. *J Neurophysiol* 29: 315-331, 1966.

34. **Esposito F, Orizio C, Parrinello G, and Veicsteinas A**. Chronic hypobaric hypoxia does not affect electro-mechanical muscle activities during sustained maximal isometric contractions. *Eur J Appl Physiol* 90: 337-343, 2003.

35. **Fulco CS, Lewis SF, Frykman PN, Boushel R, Smith S, Harman EA, Cymerman A, and Pandolf KB**. Muscle fatigue and exhaustion during dynamic leg exercise in normoxia and hypobaric hypoxia. *J Appl Physiol* 81: 1891-1900, 1996.

36. **Fulco CS, Rock PB, and Cymerman A**. Maximal and submaximal exercise performance at altitude. *Aviat Space Environ Med* 69: 793-801, 1998.

37. **Gandevia SC**. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 81: 1725-1789, 2001.

38. **Gibson GE, and Duffy TE**. Impaired synthesis of acetylcholine by mild hypoxic hypoxia or nitrous oxide. *J Neurochem* 36: 28-33, 1981.

39. **Gonzalez-Alonso J, Dalsgaard MK, Osada T, Volianitis S, Dawson EA, Yoshiga CC, and Secher NH**. Brain and central haemodynamics and oxygenation during maximal exercise in humans. *J Physiol* 557: 331-342, 2004.

40. **Goodall S, Ross EZ, and Romer LM**. Effect of graded hypoxia on supraspinal contributions to fatigue with unilateral knee-extensor contractions. *J Appl Physiol* 109: 10, 2010.

41. **Gore CJ, Hahn AG, Scroop GC, Watson DB, Norton KI, Wood RJ, Campbell DP, and Emonson DL**. Increased arterial desaturation in trained cyclists during maximal exercise at 580 m altitude. *J Appl Physiol* 80: 2204-2210, 1996.

42. **Hansen AJ**. Effect of anoxia on ion distribution in the brain. *Physiol Rev* 65: 101-148, 1985.

43. **Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, and Dempsey JA**. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 82: 1573-1583, 1997.

44. **Hill JM, Pickar JG, Parrish MD, and Kaufman MP**. Effects of hypoxia on the discharge of group III and IV muscle afferents in cats. *J Appl Physiol* 73: 2524-2529, 1992.

45. **Hilty L, Lutz K, Maurer K, Rodenkirch T, Spengler CM, Boutellier U, Jäncke L, and Amann M**. Spinal opioid receptor-sensitive muscle afferents contribute to the fatigue-induced increase in intracortical inhibition in healthy humans. *Exp Physiol* 96: 505-517, 2011.

46. **Hogan MC, Richardson RS, and Haseler LJ**. Human muscle performance and PCr hydrolysis with varied inspired oxygen fractions: a 31P-MRS study. *J Appl Physiol* 86: 1367-1373, 1999.

47. **Hohimer AR, Hales JR, Rowell LB, and Smith OA**. Regional distribution of blood flow during mild dynamic leg exercise in the baboon. *J Appl Physiol* 55: 1173-1177, 1983.

48. **Huang SY, Moore LG, McCullough RE, McCullough RG, Micco AJ, Fulco C, Cymerman A, Manco-Johnson M, Weil JV, and Reeves JT**. Internal carotid and vertebral arterial flow velocity in men at high altitude. *J Appl Physiol* 63: 395-400, 1987.

49. **Huang SY, Tawney KW, Bender PR, Groves BM, McCullough RE, McCullough RG, Micco AJ, Manco-Johnson M, Cymerman A, Greene R, and Reeves JT**. Internal carotid flow velocity with exercise before and after acclimatisation to 4300 m. *J Appl Physiol* 71: 1469-1476, 1991.

50. **Ide K, Horn A, and Secher NH**. Cerebral metabolic response to submaximal exercise. *J Appl Physiol* 87: 1604-1608, 1999.

51. **Imray CH, Myers SD, Pattinson KT, Bradwell AR, Chan CW, Harris S, Collins P, and Wright AD**. Effect of exercise on cerebral perfusion in humans at high altitude. *J Appl Physiol* 99: 699-706, 2005.

52. **Jorgensen LG, Perko G, and Secher NH**. Regional cerebral artery mean flow velocity and blood flow during dynamic exercise in humans. *J Appl Physiol* 73: 1825-1830, 1992.

53. **Kastrup A, Kruger G, Neumann-Haefelin T, Glover GH, and Moseley ME**. Changes of cerebral blood flow, oxygenation, and oxidative metabolism during graded motor activation. *Neuroimage* 15: 74-82, 2002.

54. **Katayama K, Amann M, Pegelow DF, Jacques AJ, and Dempsey JA**. Effect of arterial oxygenation on quadriceps fatigability during isolated muscle exercise. *Am J Physiol Regul Integr Comp Physiol* 292: R1279-R1286, 2007.

55. **Katayama K, Yoshitake Y, Watanabe K, Akima H, and Ishida K**. Muscle deoxygenation during sustained and intermittent isometric exercise in hypoxia. *Med Sci Sports Exerc* 42: 1269-1278, 2010.

56. **Kayser B, Narici M, Binzoni T, Grassi B, and Cerretelli P**. Fatigue and exhaustion in chronic hypobaric hypoxia: influence of exercising muscle mass. *J Appl Physiol* 76: 634-640, 1994.

57. **Kjaer M, Hanel B, Worm L, Perko G, Lewis SF, Sahlin K, Galbo H, and Secher NH**. Cardiovascular and neuroendocrine responses to exercise in hypoxia during impaired neural feedback from muscle. *Am J Physiol* 277: R76-85, 1999.

58. **Kleinschmidt A, Obrig H, Requardt M, Merboldt KD, Dirnagl U, Villringer A, and Frahm J**. Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab* 16: 817-826, 1996.

59. **Lieberman P, Protopapas A, Reed E, Youngs JW, and Kanki BG**. Cognitive defects at altitude. *Nature* 372: 325, 1994.

60. **Liu JZ, Shan ZY, Zhang LD, Sahgal V, Brown RW, and Yue GH**. Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an FMRI study. *J Neurophysiol* 90: 300-312, 2003.

61. **Lucas SJ, Burgess KR, Thomas KN, Donnelly J, Peebles KC, Lucas RA, Fan JL, Cotter JD, Basnyat R, and Ainslie PN**. Alterations in cerebral blood flow and cerebrovascular reactivity during 14 days at 5050 m. *J Physiol* 589: 741-753, 2011.

62. **Madsen PL, Sperling BK, Warming T, Schmidt JF, Secher NH, Wildschiodtz G, Holm S, and Lassen NA**. Middle cerebral artery blood velocity and cerebral blood flow and O2 uptake during dynamic exercise. *J Appl Physiol* 74: 245-250, 1993.

63. **Marcora SM, Staiano W, and Manning V**. Mental fatigue impairs physical performance in humans. *J Appl Physiol* 106: 857-864, 2009.

64. **Millet GY, Aubert D, Favier FB, Busso T, and Benoit H**. Effect of acute hypoxia on central fatigue during repeated isometric leg contractions. *Scand J Med Sci Sports* 19: 695, 2009.

65. **Millet GY, Martin V, Lattier G, and Ballay Y**. Mechanisms contributing to knee extensor strength loss after prolonged running exercise. *J Appl Physiol* 94: 193-198, 2003.

66. **Millet GY, Martin V, Martin A, and Verges S**. Electrical stimulation for testing neuromuscular function: from sport to pathology. *Eur J Appl Physiol* 111: 2489-2500, 2011.

67. **Millet GY, Muthalib M, Jubeau M, Laursen PB, and Nosaka K**. Severe hypoxia affects exercise performance independently of afferent feedback and peripheral fatigue. *J Appl Physiol* in press.

68. **Miscio G, Milano E, Aguilar J, Savia G, Foffani G, Mauro A, Mordillo-Mateos L, Romero-Ganuza J, and Oliviero A**. Functional involvement of central nervous system at high altitude. *Exp Brain Res* 194: 157-162, 2009.

69. **Miyamoto O, and Auer RN**. Hypoxia, hyperoxia, ischemia, and brain necrosis. *Neurology* 54: 362-371, 2000.

70. **Mohamed-Hussein AA, Hamed SA, and Abdel-Hakim N**. Cerebral cortical dysfunction in chronic obstructive pulmonary disease: role of transcranial magnetic stimulation. *Int J Tuberc Lung Dis* 11: 515-521, 2007.

71. **Moller K, Paulson OB, Hornbein TF, Colier WN, Paulson AS, Roach RC, Holm S, and Knudsen GM**. Unchanged cerebral blood flow and oxidative metabolism after acclimatization to high altitude. *J Cereb Blood Flow Metab* 22: 118-126, 2002.

72. **Neubauer JA, Melton JE, and Edelman NH**. Modulation of respiration during brain hypoxia. *J Appl Physiol* 68: 441-451, 1990.

73. **Neubauer JA, and Sunderram J**. Oxygen-sensing neurons in the central nervous system. *J Appl Physiol* 96: 367-374, 2004.

74. **Nishimura N, Iwasaki K, Ogawa Y, and Aoki K**. Decreased steady-state cerebral blood flow velocity and altered dynamic cerebral autoregulation during 5-h sustained 15% O2 hypoxia. *J Appl Physiol* 108: 1154-1161, 2010.

75. **Nybo L, and Rasmussen P**. Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. *Exerc Sport Sci Rev* 35: 110-118, 2007.

76. **Oliviero A, Corbo G, Tonali PA, Pilato F, Saturno E, Dileone M, Versace V, Valente S, and Di Lazzaro V**. Functional involvement of central nervous system in acute exacerbation of chronic obstructive pulmonary disease A preliminary transcranial magnetic stimulation study. *J Neurol* 249: 1232-1236, 2002.

77. **Olson EB, Jr., Vidruk EH, McCrimmon DR, and Dempsey JA**. Monoamine neurotransmitter metabolism during acclimatization to hypoxia in rats. *Respir Physiol* 54: 79-96, 1983.

78. **Ozaki H, Watanabe S, and Suzuki H**. Topographic EEG changes due to hypobaric hypoxia at simulated high altitude. *Electroencephalogr Clin Neurophysiol* 94: 349-356, 1995.

79. **Papadelis C, Kourtidou-Papadeli C, Bamidis PD, Maglaveras N, and Pappas K**. The effect of hypobaric hypoxia on multichannel EEG signal complexity. *Clin Neurophysiol* 118: 31-52, 2007.

80. **Peltonen JE, Kowalchuk JM, Paterson DH, DeLorey DS, duManoir GR, Petrella RJ, and Shoemaker JK**. Cerebral and muscle tissue oxygenation in acute hypoxic ventilatory response test. *Respir Physiol Neurobiol* 155: 71-81, 2007.

81. **Peltonen JE, Paterson DH, Shoemaker JK, Delorey DS, Dumanoir GR, Petrella RJ, and Kowalchuk JM**. Cerebral and muscle deoxygenation, hypoxic ventilatory chemosensitivity and cerebrovascular responsiveness during incremental exercise. *Respir Physiol Neurobiol* 169: 24-35, 2009.

82. **Peltonen JE, Rusko HK, Rantamaki J, Sweins K, Niittymaki S, and Viitasalo JT**. Effects of oxygen fraction in inspired air on force production and electromyogram activity during ergometer rowing. *Eur J Appl Physiol* 76: 495-503, 1997.

83. **Perrey S, and Rupp T**. Altitude-induced changes in muscle contractile properties. *High Alt Med Biol* 10: 175-182, 2009.

84. **Post M, Steens A, Renken R, Maurits NM, and Zijdewind I**. Voluntary activation and cortical activity during a sustained maximal contraction: an fMRI study. *Human brain mapping* 30: 1014-1027, 2009.

85. **Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, and Gjedde A**. Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J Cereb Blood Flow Metab* 27: 1082-1093, 2007.

86. **Rasmussen P, Nielsen J, Overgaard M, Krogh-Madsen R, Gjedde A, Secher NH, and Petersen NC**. Reduced muscle activation during exercise related to brain oxygenation and metabolism in humans. *J Physiol* 588: 1985-1995, 2010.

87. **Romer LM, Haverkamp HC, Amann M, Lovering AT, Pegelow DF, and Dempsey JA**. Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. *Am J Physiol Regul Integr Comp Physiol* 292: R598-606, 2007.

88. **Romer LM, Haverkamp HC, Lovering AT, Pegelow DF, and Dempsey JA**. Effect of exercise-induced arterial hypoxemia on quadriceps muscle fatigue in healthy humans. *Am J Physiol Regul Integr Comp Physiol* 290: R365-375, 2006.

89. **Romer LM, Lovering AT, Haverkamp HC, Pegelow DF, and Dempsey JA**. Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans. *J Physiol* 571: 425-439, 2006.

90. **Rooks CR, Thom NJ, McCully KK, and Dishman RK**. Effects of incremental exercise on cerebral oxygenation measured by near-infrared spectroscopy: a systematic review. *Prog Neurobiol* 92: 134-150, 2010.

91. **Rupp T, and Perrey S**. Effect of severe hypoxia on prefrontal and muscle oxygentaion responses at rest and during isometric exhausting exercise. *Adv Exp Med Biol* 645: 329-334, 2009.

92. **Rupp T, and Perrey S**. Prefrontal cortex oxygenation and neuromuscular responses to exhaustive exercise. *Eur J Appl Physiol* 102: 153-163, 2008.

93. **Saito S, Nishihara F, Takazawa T, Kanai M, Aso C, Shiga T, and Shimada H**. Exercise-induced cerebral deoxygenation among untrained trekkers at moderate altitudes. *Arch Environ Health* 54: 271-276, 1999.

94. **Savard GK, Areskog NH, and Saltin B**. Maximal muscle activation is not limited by pulmonary ventilation in chronic hypoxia. *Acta Physiol Scand* 157: 187-190, 1996.

95. **Schoonman GG, Sandor PS, Nirkko AC, Lange T, Jaermann T, Dydak U, Kremer C, Ferrari MD, Boesiger P, and Baumgartner RW**. Hypoxia-induced acute mountain sickness is associated with intracellular cerebral edema: a 3 T magnetic resonance imaging study. *J Cereb Blood Flow Metab* 28: 198-206, 2008.

96. **Secher NH, Seifert T, and Van Lieshout JJ**. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol* 104: 306-314, 2008.

97. **Severinghaus JW, Chiodi H, Eger EI, 2nd, Brandstater B, and Hornbein TF**. Cerebral blood flow in man at high altitude. Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. *Circ Res* 19: 274-282, 1966.

98. **Smith JL, Martin PG, Gandevia SC, and Taylor JL**. Sustained contraction at very low forces produces prominent supraspinal fatigue in human elbow flexor muscles. *J Appl Physiol* 103: 560-568, 2007.

99. **Subudhi AW, Dimmen AC, Julian CG, Wilson MJ, Panerai RB, and Roach RC**. Effects of acetazolamide and dexamethasone on cerebral hemodynamics in hypoxia. *J Appl Physiol* 110: 1219-1265, 2011.

100. **Subudhi AW, Dimmen AC, and Roach RC**. Effects of acute hypoxia on cerebral and muscle oxygenation during incremental exercise. *J Appl Physiol* 103: 177-183, 2007.

101. **Subudhi AW, Lorenz MC, Fulco CS, and Roach RC**. Cerebrovascular responses to incremental exercise during hypobaric hypoxia: effect of oxygenation on maximal performance. *Am J Physiol Heart Circ Physiol* 294: H164-171, 2008.

102. **Subudhi AW, Miramon BR, Granger ME, and Roach RC**. Frontal and motor cortex oxygenation during maximal exercise in normoxia and hypoxia. *J Appl Physiol* 106: 1153-1158, 2009.

103. **Subudhi AW, Olin JT, Dimmen AC, Polaner DM, Kayser B, and Roach RC**. Does cerebral oxygen limit incremental exercise performance ? *J Appl Physiol* in press: 2012.

104. **Szubski C, Burtscher M, and Loscher WN**. The effects of short-term hypoxia on motor cortex excitability and neuromuscular activation. *J Appl Physiol* 101: 1673-1677, 2006.

105. **Szubski C, Burtscher M, and Loscher WN**. Neuromuscular fatigue during sustained contractions performed in short-term hypoxia. *Med Sci Sports Exerc* 39: 948-954, 2007.

106. **Taylor AD, Bronks R, Smith P, and Humphries B**. Myoelectric evidence of peripheral muscle fatigue during exercise in severe hypoxia: some references to m. vastus

lateralis myosin heavy chain composition. *Eur J Appl Physiol Occup Physiol* 75: 151-159, 1997.

107. **Taylor JL, Allen GM, Butler JE, and Gandevia SC**. Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. *J Appl Physiol* 89: 305-313, 2000.

108. **Todd G, Taylor JL, and Gandevia SC**. Measurement of voluntary activation of fresh and fatigued human muscles using transcranial magnetic stimulation. *J Physiol* 551: 661-671, 2003.

109. **Torre-Bueno JR, Wagner PD, Saltzman HA, Gale GE, and Moon RE**. Diffusion limitation in normal humans during exercise at sea level and simulated altitude. *J Appl Physiol* 58: 989-995, 1985.

110. **Tuunanen PI, and Kauppinen RA**. Effects of oxygen saturation on BOLD and arterial spin labelling perfusion fMRI signals studied in a motor activation task. *Neuroimage* 30: 102-109, 2006.

111. **Verges S, Bachasson D, and Wuyam B**. Effect of acute hypoxia on respiratory muscle fatigue in healthy humans. *Respir Res* 11: 109, 2010.

112. **Virues-Ortega J, Buela-Casal G, Garrido E, and Alcazar B**. Neuropsychological functioning associated with high-altitude exposure. *Neuropsychol Rev* 14: 197-224, 2004.

113. **Vivodtzev I, Flore P, Levy P, and Wuyam B**. Voluntary activation during knee extensions in severely deconditioned patients with chronic obstructive pulmonary disease: benefit of endurance training. *Muscle Nerve* 37: 27-35, 2008.

114. **Volianitis S, Fabricius-Bjerre A, Overgaard A, Stromstad M, Bjarrum M, Carlson C, Petersen NT, Rasmussen P, Secher NH, and Nielsen HB**. The cerebral metabolic ratio is not affected by oxygen availability during maximal exercise in humans. *J Physiol* 586: 107-112, 2008.

115. **Wagner PD**. Reduced maximal cardiac output at altitude--mechanisms and significance. *Respir Physiol* 120: 1-11, 2000.

116. **Werhahn KJ, Kunesch E, Noachtar S, Benecke R, and Classen J**. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 517 (Pt 2): 591-597, 1999.

117. **Willer JC, Miserocchi G, and Gautier H**. Hypoxia and monosynaptic reflexes in humans. *J Appl Physiol* 63: 639-645, 1987.

118. **Wilson MH, Edsell ME, Davagnanam I, Hirani SP, Martin DS, Levett DZ, Thornton JS, Golay X, Strycharczuk L, Newman SP, Montgomery HE, Grocott MP, and Imray CH**. Cerebral artery dilatation maintains cerebral oxygenation at extreme altitude and in acute hypoxia-an ultrasound and MRI study. *J Cereb Blood Flow Metab* 31: 2019-2029, 2011.

FIGURE LEGENDS

Figure 1. Representative recordings of arterial oxygen saturation (SaO_2), end-tidal CO_2 partial pressure ($PETCO_2$), middle cerebral artery blood flow velocity (MCAV) and blood pressure (BP) at rest and during submaximal exercise in normoxia and hypoxia ($FiO_2 = 0.12$ (rest) or 0.14 (exercise)) (from (2))

Figure 2. Changes in brain (prefrontal) and muscle oxyhemoglobin (A), deoxyhemoglobin (B) and total hemoglobin (C) concentrations during normoxic and hypoxic (hatched columns) conditions at rest and during submaximal cycling. Values are means ± SD. * Different from muscle ($P \leq 0.05$); † Different from hypoxic rest at all time points ($P \leq 0.05$); $^{\theta}$ Different from pre-exercise ($P \leq 0.05$) (from (2))

Figure 3. Representative changes in cerebral (A) and muscle (B) oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) from a single subject performing incremental exercise to maximal exertion at sea level (thick solid line), acute hypoxia (thick shaded line) and chronic hypoxia (thin solid line). Arrows mark the gas switch to $FiO_2 = 0.60$. (from (101))

Figure 4. Cortical voluntary activation measured using TMS at baseline in normoxia (BL), after a 10-min wash-in period with the test gas (Wash-in), at the end of the fatiguing protocol (0) and up to 45 min after intermittent knee extensions to task failure performed with various inspiratory O_2 fractions (from 0.10 to 0.21). Values are means ± SE. * $P < 0.05$, all conditions vs. BL. † $P < 0.05$, $FiO_2 = 0.10$ vs. $FiO_2 = 0.21$ (from (40))

Figure 5. Quadriceps fatigue and integrated EMG (iEMG) during cycling at 333 ± 9 W in normoxia and two levels of hypoxia, with hyperoxia at exhaustion. *Panel A*: post-exercise reduction in potentiated quadriceps twitch; * $P < 0.05$ from $FiO_2 = 0.15$ and 0.30, † $P < 0.05$ from $FiO_2 = 0.10$, 0.15 and 0.30. *Panel B*: iEMG of the *vastus lateralis* as a percentage of the first minute of exercise; filled symbols represent values obtained in the respective FiO_2 condition (0.21/0.15/0.10), open symbols indicate iEMG values obtained at exhaustion after the switch to the hyperoxic inspirate ($FiO_2 = 0.30$); * $P < 0.05$ from previous value. † $P < 0.05$ from normoxia at isotime. (from (13))

Figure 6. Schematic representation of the main potential mechanisms that may link reduced arterial oxygenation to altered central motor drive during hypoxic exercise. Reduced arterial oxygenation and CO_2 can affect cerebral blood flow and oxygenation; changes in cerebral oxygenation and its cellular consequences may modify neuronal excitability and finally central drive to the muscles. Interactions between working muscles and the brain may also be involved, *i.e.* competition for blood flow distribution and increased afferent muscle signals.

Table 1. Changes in cerebral blood flow and oxygenation during exercise in hypoxic conditions compared to normoxic conditions

Ref	Hypoxic condition	Exercise characteristics	*Hypoxia vs. normoxia* Cerebral blood flow (MCAV*)	Cerebral oxygenation
(91)	Acute hypoxia (FiO_2 = 0.11, ~4700 m)	Sustained ankle extension at 40% MVC		↓ HbO_2 and ↓ HbTot
(110)	Acute hypoxia (FiO_2 = 0.12, ~4100 m)	Finger tapping (2 Hz)	↓ (MRI ASL signal)	↓ (MRI BOLD signal)
(49)	Acute (PiO_2 = 83 Torr, ~4300 m) and chronic (18 days at 4300 m) hypoxia	Cycling at low (same absolute workload), middle and high (same relative workload) intensities for 5 min	↓ at same absolute and relative workload in chronic hypoxia only	
(2)	Acute hypoxia (FiO_2 = 0.14, ~3000 m)	Cycling at 60-70% of normoxic maximal O_2 uptake for 5 min	=	↑ HHb and ↑ HbTot
(86)	Acute hypoxia (FiO_2 = 0.10, ~5300 m)	Cycling at high intensity in hypoxia and at the same absolute or relative intensity in hypoxia	↑ at same absolute and relative workload	↓ O_2 delivery and $PmitoO_2$ at same absolute and relative workload
(100)	Acute hypoxia (FiO_2 = 0.12, ~4100 m)	Incremental maximal cycling		↓ HbO_2, ↑ HHb and ↓ HbTot at same relative and absolute (except HbTot) workload
(102)	Acute hypoxia (PiO_2 = 79 mmHg, ~4700 m)	Incremental maximal cycling	↑ at maximal intensity	↓ HbO_2 at same absolute workload
(81)	Acute hypoxia (PiO_2 = 118 mmHg, ~2500 m)	Incremental maximal cycling	= at same absolute and maximal workload	↓ HbO_2 and ↑ HHb at same absolute workload
(101)	Acute and chronic (1 week) hypoxia (PiO_2 = 86 Torr, 4300 m)	Incremental maximal cycling	↑ at maximal intensity in chronic hypoxia only	↓ HbO_2 and ↑ HHb at maximal intensity

(51)	Chronic hypoxia (after 24-36h at 3610 m, within 9 days at 4750m and 5260 m)	Incremental maximal cycling	↑ at same relative workload (at 4750 and 5260 m only)	↑ HHb at same relative workload
(93)	Chronic hypoxia (2700 and 3700 m)	Stepping at moderate intensity (same absolute workload)		↓ cerebral O_2 saturation (NIRS)

PiO_2, partial O_2 inspiratory pressure; FiO_2, inspiratory O_2 fraction; MCAV, middle cerebral artery blood velocity; HHb, exercise-induced changes in cerebral deoxygenated heme concentration; HbO_2, exercise-induced changes in cerebral oxygenated heme concentration; HbTot, exercise-induced changes in cerebral total heme concentration; $PmitoO_2$, mitochondrial oxygen tension; *, except ref [110].

Table 2. EMG changes during exercise in hypoxic conditions compared to normoxic conditions

Ref	Hypoxic condition	Exercise modality	Exercise intensity, duration	EMG changes in hypoxia vs. normoxia
			Isolated exercise	
(35)	Acute hypoxia (barometric pressure = 464 Torr, ~ 4300 m)	Dynamic 1-leg knee extension (90-150°, 1 Hz), MVCs every 2 min during the test	Submaximal constant load at the same absolute load (21 ± 3 W, i.e. 62 ± 3 and 79 ± 2% of 1-leg peak work rate for normoxia and hypobaria, respectively) to exhaustion	Greater rise in iEMG during submaximal contractions and greater fall in iEMG during MVCs at isotime ; similar iEMG changes during submaximal contractions and MVC at exhaustion
(54)	Acute hypoxia (FiO_2 = 0.11, ~4700 m)	Intermittent (5s on - 5s off) isometric 1-leg knee extension, MVCs before and after each set	Submaximal constant load (at 62% MVC), 3 sets of 9 contractions	Greater rise in iEMG during submaximal contractions and similar fall in iEMG during MVCs at isotime
(55)	Acute hypoxia (FiO_2 = 0.10-0.12, ~4700 m; target SpO_2 = 75-80%)	Intermittent (5s on -5s off) isometric 1-leg knee extension	Submaximal intensity (60% MVC) to exhaustion	Greater rise in iEMG at isotime and at exhaustion
		Sustained isometric 1-leg knee extension	Submaximal intensity (60% MVC) to exhaustion	Similar rise in iEMG at isotime and at exhaustion
(31)	Acute hypoxia (FiO_2 = 0.15, ~ 2500 m)	Sustained isometric handgrip	Submaximal intensity (60% MVC) to exhaustion	Blunted rise in RMS (N.S.)
(64)	Acute hypoxia (FiO_2 = 0.11, ~4700 m)	Intermittent (10s on - 10s off) isometric 1-leg knee extension	Submaximal intensity (50% MVC) to exhaustion	Similar increase in RMS
(56)	Chronic hypoxia (1 month at 5050 m)	Dynamic forearm flexion (5-cm amplitude, 0.5 Hz)	Submaximal constant-load test (at 30% 1-RM) to exhaustion	Similar rise in iEMG at isotime and at exhaustion
(34)	Chronic hypoxia (43 days at 5050 m)	Sustained knee or elbow extension	MVC for 1 min	Similar reduction in RMS

		Whole body exercise		
(12)	Acute hypoxia (FiO_2 = 0.15, ~ 2500 m)	Cycling	Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 82% normoxic maximal power output) for the same duration (= maximal duration in hypoxia)	Greater rise in iEMG at isotime
(106)	Acute hypoxia (FiO_2 = 0.12, ~ 4100 m)	Cycling, MVCs before and after	Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 77% normoxic age-predicted maximal heart rate) for 10 min	Greater rise in iEMG at isotime, similar iEMG during MVCs before and after cycling
(13)	Acute hypoxia (FiO_2 = 0.10 and 0.15, ~4700m and ~ 2500 m)	Cycling	Submaximal constant-load intensity (same absolute workload in normoxia and hypoxia: 81% normoxic maximal power output) to exhaustion	Greater rise in iEMG at isotime and smaller rise at exhaustion in severe hypoxia only
(7)	Acute hypoxia (FiO_2 = 0.15, ~ 2500 m)	Cycling	5-km time-trial	Smaller iEMG
(56)	Chronic hypoxia (1 month at 5050 m)	Cycling	Local maximal workload (workload hypoxia = ~80% workload normoxia) to exhaustion	Blunted rise in iEMG at isotime and at exhaustion

FiO_2, inspiratory O_2 fraction; MVC, maximal voluntary contraction; iEMG, integrated EMG signal; RMS: Root Mean Square of EMG signal; N.S. non significant

Figure 1.

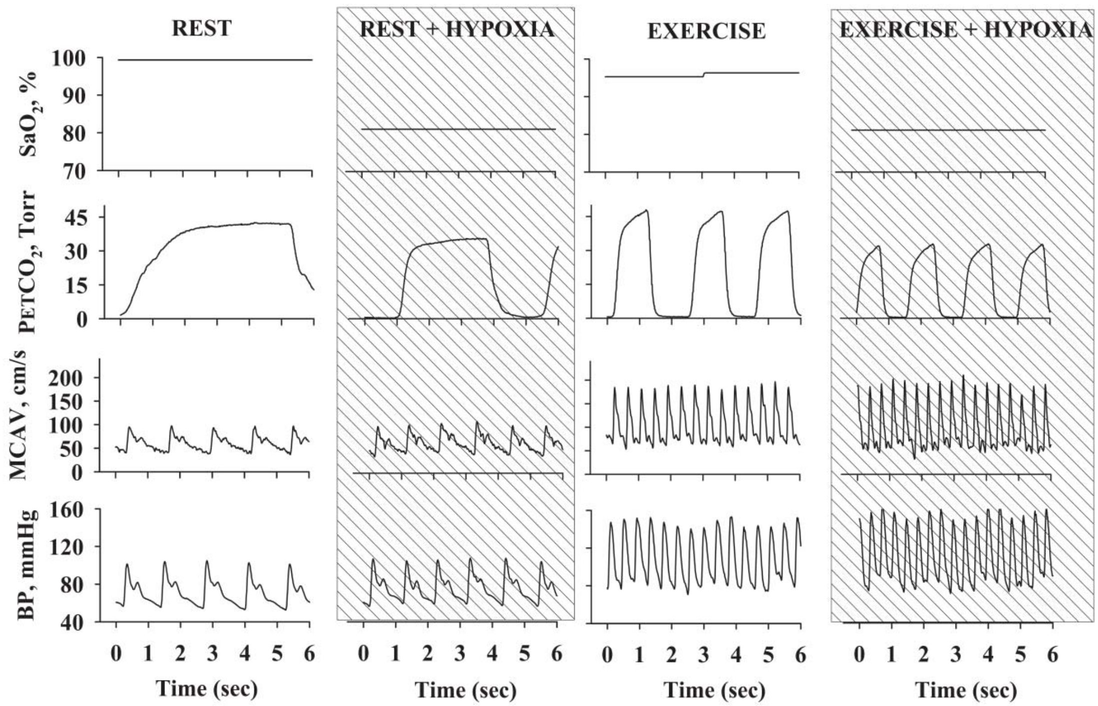
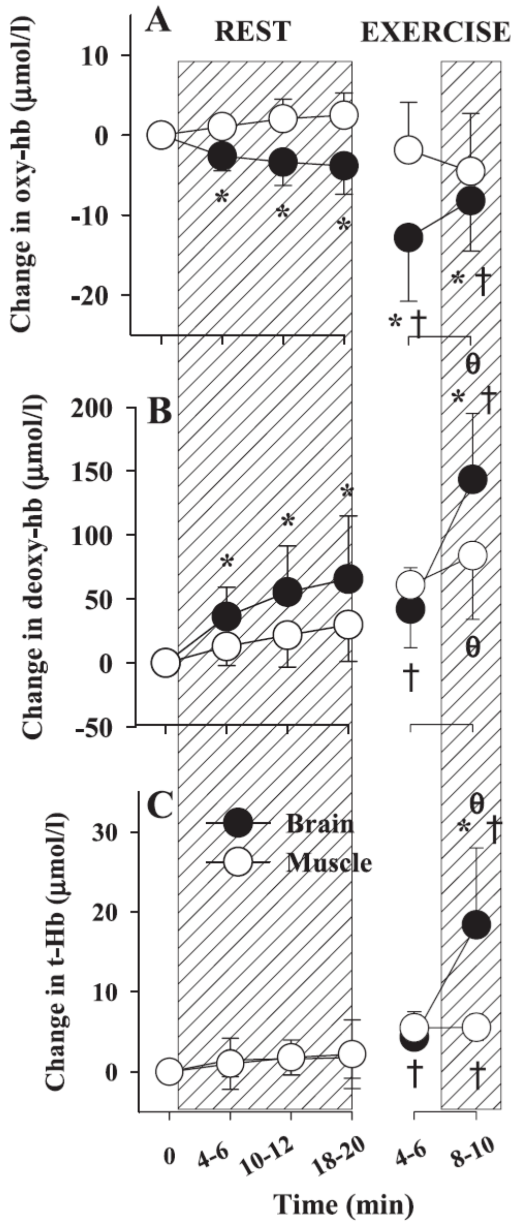

REST
REST + HYPOXIA
EXERCISE
EXERCISE + HYPOXIA
SaO2, %
100
90
80
70
PETCO2, Torr
45
30
15
0
MCAV, cm/s
200
150
100
50
0
BP, mmHg
160
120
80
40
0 1 2 3 4 5 6
Time (sec)
Time (sec)
Time (sec)
Time (sec)

Figure 2.



A
REST
EXERCISE
Change in oxy-hb (µmol/l)
10
0
-10
-20
B
Change in deoxy-hb (µmol/l)
200
150
100
50
0
-50
C
Brain
Muscle
Change in t-Hb (µmol/l)
30
20
10
0
0
4-6
10-12
18-20
4-6
8-10
Time (min)

Figure 3.

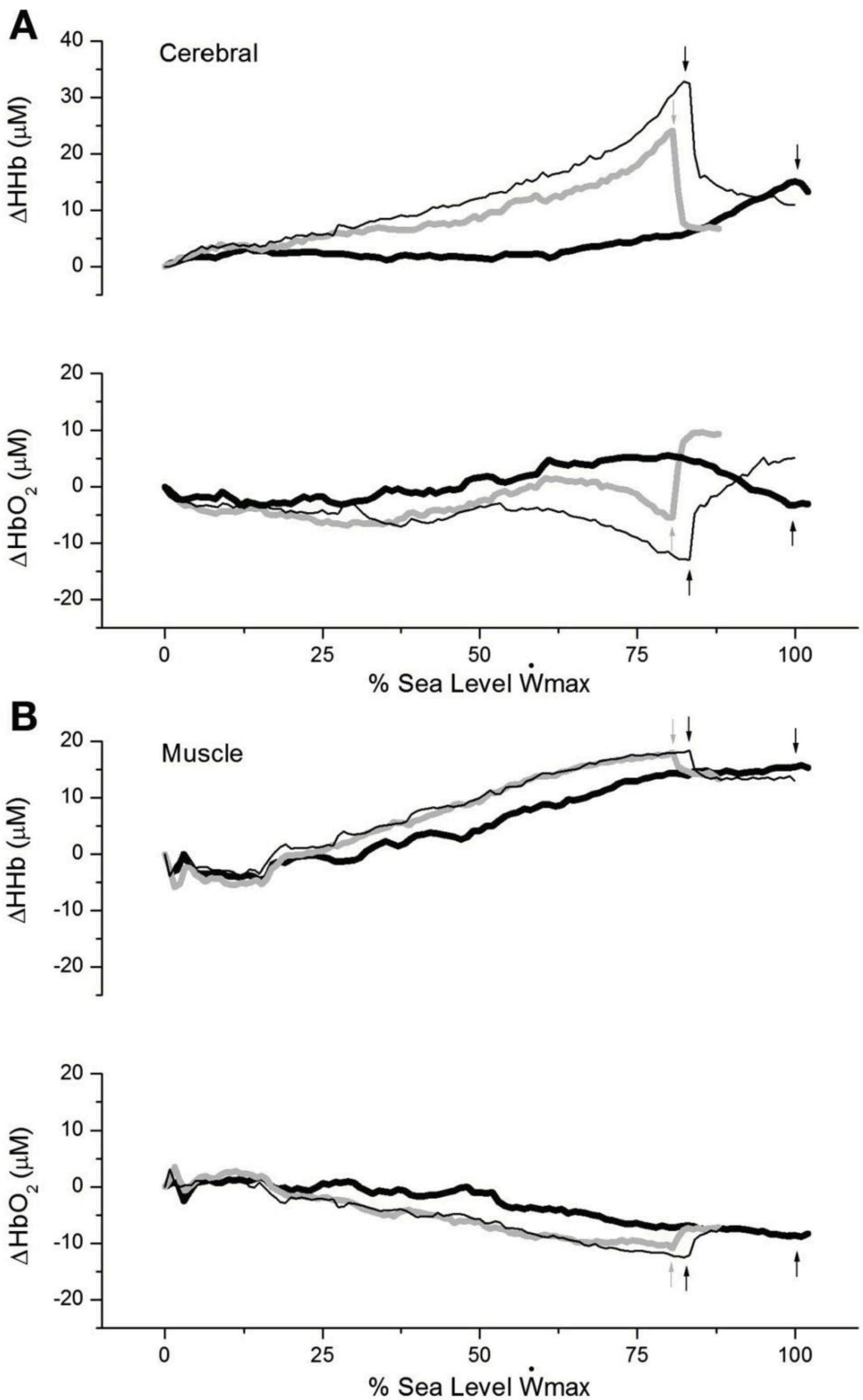
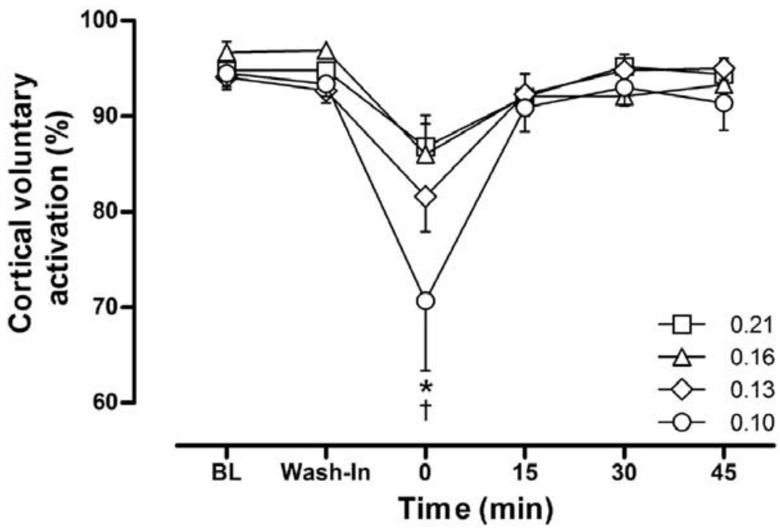
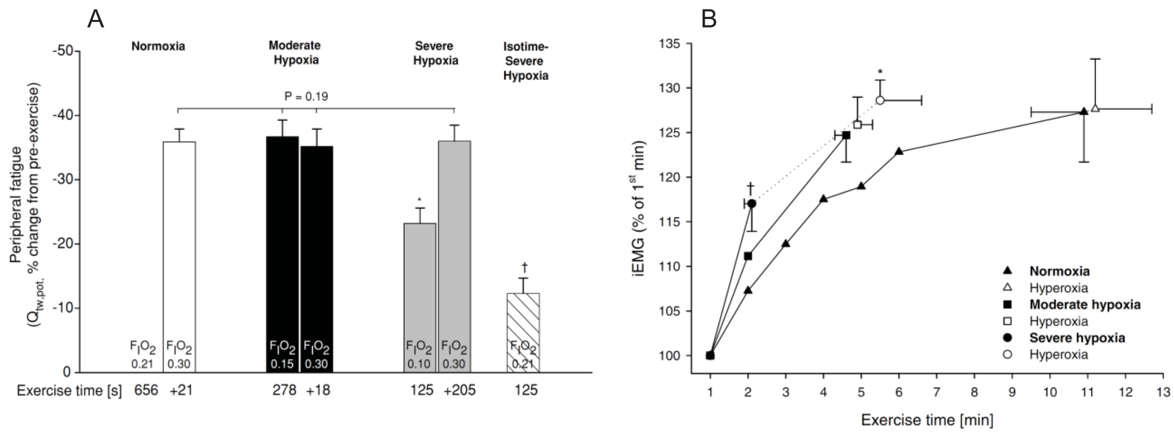

A
Cerebral
40
30
20
10
0
ΔHHb (μM)
20
10
0
-10
-20
ΔHbO2 (μM)
0
25
50
75
100
% Sea Level Ẇmax
B
Muscle
20
10
0
-10
-20
ΔHHb (μM)
20
10
0
-10
-20
ΔHbO2 (μM)
0
25
50
75
100
% Sea Level Ẇmax

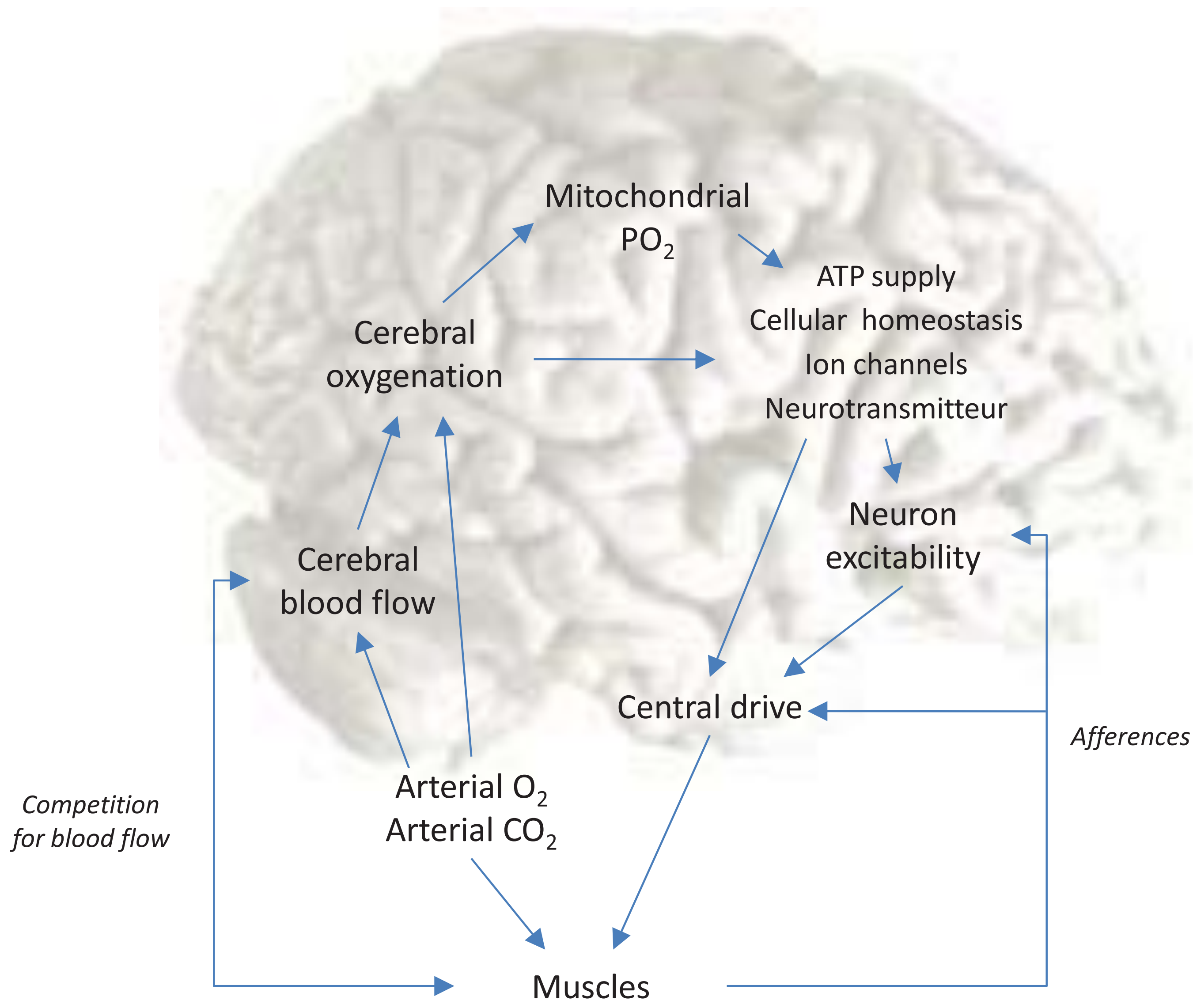
Figure 4.



Cortical voluntary activation (%)
100
90
80
70
60
*
†
0.21
0.16
0.13
0.10
BL
Wash-In
0
15
30
45
Time (min)

Figure 5.


A
Normoxia
Moderate Hypoxia
Severe Hypoxia
Isotime-Severe Hypoxia
P = 0.19
Peripheral fatigue
($Q_{tw,pot.}$ % change from pre-exercise)
F_IO_2 0.21
F_IO_2 0.30
F_IO_2 0.15
F_IO_2 0.30
F_IO_2 0.10
F_IO_2 0.30
F_IO_2 0.21
Exercise time [s] 656 +21 278 +18 125 +205 125
B
iEMG (% of 1st min)
Normoxia
Hyperoxia
Moderate hypoxia
Hyperoxia
Severe hypoxia
Hyperoxia
Exercise time [min]



Mitochondrial PO$_2$
ATP supply
Cellular homeostasis
Ion channels
Neurotransmitteur
Cerebral oxygenation
Neuron excitability
Cerebral blood flow
Central drive
Afferences
Competition for blood flow
Arterial O$_2$
Arterial CO$_2$
Muscles